

Current Literature

In Clinical Science



Brivaracetam, a Novel Antiepileptic Drug: Is it Effective and Safe? Results from One Phase III Randomized Trial

Brivaracetam as Adjunctive Treatment for Uncontrolled Partial Epilepsy in Adults: A Phase III Randomized, Double-Blind, Placebo-Controlled Trial.

Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. *Epilepsia* 2014;55:57–66

PURPOSE: Brivaracetam (BRV) is a novel high-affinity synaptic vesicle protein 2A ligand currently being investigated for the treatment of epilepsy. The purpose of this phase III study was to evaluate the efficacy and safety/tolerability of adjunctive BRV in adults with uncontrolled partial-onset (focal) seizures. **METHODS:** This was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial (N01253; NCT00464269). Adults aged 16–70 years with well-characterized partial epilepsy not fully controlled despite treatment with one or two antiepileptic drugs (AEDs) were enrolled. Patients who experienced eight or more partial-onset seizures, whether or not secondarily generalized, during the 8-week prospective baseline period were randomized (1:1:1:1) to receive twice-daily placebo (PBO) or BRV (5, 20, or 50 mg/day) without titration. The primary efficacy endpoint was percent reduction over PBO in baseline-adjusted partial-onset seizure frequency/week during the 12-week treatment period. Comparison of BRV with PBO was sequential (50, 20 mg/day, then 5 mg/day). Secondary endpoints included $\geq 50\%$ responder rate and median percent reduction from baseline in partial-onset seizure frequency/week. Post hoc analyses included the primary efficacy endpoint evaluated over 28 days and exploratory subanalyses of efficacy by seizure subtype. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs), laboratory tests, electrocardiography, vital signs, and physical and neurologic examinations. **KEY FINDINGS:** Of 400 patients randomized, 396 were included in the intent-to-treat (ITT) population (PBO $n = 98$, BRV 5 mg/day $n = 97$, BRV 20 mg/day $n = 100$, BRV 50 mg/day $n = 101$) and 392 comprised the modified ITT (mITT) population. A total of 361 (91.2%) of 396 patients completed the study. Most patients (78.3%) were receiving two concomitant AEDs. Percent reduction in partial-onset seizure frequency/week over PBO was -0.9% ($p = 0.885$) for BRV 5 mg/day, 4.1% ($p = 0.492$) for BRV 20 mg/day, and 12.8% ($p = 0.025$) for BRV 50 mg/day (mITT population). Statistical significance was also achieved for the percent reduction over PBO in baseline-adjusted partial-onset seizure frequency/28 days for BRV 50 mg/day (22.0% ; $p = 0.004$) but not for the other BRV dose groups. In the BRV 50 mg/day group, statistical significance was also seen for the $\geq 50\%$ responder rate (BRV 32.7% vs. PBO 16.7% ; $p = 0.008$) and median percent reduction from baseline in partial-onset seizure frequency/week (BRV 30.5% vs. PBO 17.8% ; $p = 0.003$). In the exploratory subanalysis by seizure subtype, median percent reduction from baseline in seizure frequency/week and $\geq 50\%$ responder rate were numerically greater than PBO in the BRV 20 and 50 mg/day groups for simple partial, complex partial, and secondarily generalized seizures. BRV was generally well tolerated, with the majority of TEAEs being mild-to-moderate in intensity. Of the TEAEs reported by $\geq 5\%$ patients, those with a frequency $> 3\%$ higher than PBO for any dose of BRV compared with PBO were somnolence, dizziness, fatigue, influenza, insomnia, nasopharyngitis, vomiting, diarrhea, urinary tract infection, and nausea. **SIGNIFICANCE:** Adjunctive BRV at a daily dose of 50 mg was associated with statistically significant reductions in seizure frequency compared with PBO. All doses of BRV showed good tolerability throughout the study.

Commentary

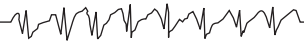
Despite the availability of multiple AEDs, many patients with epilepsy continue to have refractory seizures as well as debilitating side effects. As such, there continues to be a need to explore and investigate new AEDs. Brivaracetam is a novel

compound that has been studied extensively in preclinical, phase II, and now phase III trials. The results of three phase III, prospective multicenter randomized, double-blind placebo-controlled, parallel-group trials have recently been published (1–3) and yield mixed results.

Brivaracetam is a high-affinity synaptic vesicle protein 2A (SV2A) ligand. It is not entirely clear how SV2A affects neurotransmission, but animal studies suggest that it is potentially a good target for seizure control. Mice deficient in SV2A have seizures (4). Among animal models of epileptogenesis as well

Epilepsy Currents, Vol. 14, No. 4 (July/August) 2014 pp. 196–198
© American Epilepsy Society

OPEN  ACCESS Freely available online



as in humans with epilepsy, pathologic reduced SV2A expression is evident (5). In addition, studies find that SV2A binding strongly correlates with antiepileptic potency (6). Interestingly, levetiracetam, which is one of the most commonly used AEDs worldwide, has SV2A binding affinity. Brivaracetam by comparison, has a >30-fold affinity for SV2A than levetiracetam (7) suggesting that brivaracetam may be a very effective AED. As with most AEDs, brivaracetam likely has multiple mechanisms of action. Not only is it an SV2A ligand, it displays inhibitory activity at neuronal voltage-dependent sodium channels (8).

Early studies have generated important information about efficacy, tolerability, and pharmacologic characteristics. Preclinical studies demonstrated efficacy in animal models of partial onset seizures as well as generalized seizures (9). Pharmacokinetic studies reveal an almost 100% bioavailability. Brivaracetam is less than 20% protein bound. The drug is absorbed through the gastrointestinal tract, unaffected by food. Two phase IIb studies demonstrated efficacy as well as tolerability (10, 11). Doses studied range from 50 to 150 mg/day in equally divided doses. One study evaluating brivaracetam at 50 mg/day compared with placebo found that brivaracetam significantly reduced baseline adjusted partial-onset seizure frequency/week (10). In the second phase IIb study, brivaracetam at doses of 50 and 150 mg/day resulted in a significant reduction in baseline adjusted partial onset seizures when compared with placebo, but no difference was found between the two doses (11). Given these positive results, multiple phase III studies were designed to continue the study of brivaracetam. Biton and colleagues (1) report the findings of one of these studies.

In the reported prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, confirmatory trial, subjects aged 16 to 70 with well-characterized partial epilepsy having two or more partial-onset seizures/month in 3 months prior to screening and eight or more seizures during an 8-week prospective baseline period were randomized equally to either brivaracetam 5, 20, 50 mg/day or placebo. Of 509 patients from 85 sites, 400 were randomized. Four were subsequently excluded (one failed to take medication and three because of randomization errors) leaving a total of 396 for the intent-to-treat (ITT) population. All of these patients took at least one dose of brivaracetam. Subsequently, an additional four were excluded from the ITT population: three because of site noncompliance issues and one was identified as a clinical outlier prior to the unblinding process. The modified ITT (mITT) sample size was therefore 392. The mITT group was used for efficacy analyses, whereas the ITT group was used for safety analyses. From the mITT group, 361 completed the study. More than 85% of patients entered the long-term, open-label, follow-up study. Baseline demographics and epilepsy characteristics were similar across the treatment groups. Most subjects in the ITT population (78.3%) were taking two concomitant AEDs. Given that levetiracetam also has SV2A binding affinity, enrollment of subjects taking this agent was limited to 20% of all randomized patients.

Multiple endpoints were assessed. The primary efficacy endpoint was percent reduction over placebo in baseline-adjusted partial-onset seizure frequency/week during a 12-week treatment period. Significant reductions in partial-

onset seizure frequency/week over placebo was demonstrated in the 50 mg/day group (12.8% reduction, $p = 0.025$) and not the other groups. Secondary endpoints included $\geq 50\%$ responder rate and median percent reduction from baseline in partial-onset seizure frequency/week. Similar to the primary endpoint, only the 50 mg/day brivaracetam group achieved significance for both secondary endpoints. Post hoc analyses were also performed: primary efficacy endpoint over 28 days and exploratory subanalyses of efficacy by seizure subtype. Not surprisingly, significance was found in the percent reduction over placebo in baseline-adjusted partial-onset seizure frequency/28 days in the brivaracetam 50 mg/day group. The seizure type subanalysis revealed a significant reduction in simple partial, complex partial, and secondary generalized tonic clonic seizures when comparing both the brivaracetam 20 and 50 mg/day groups with placebo.

Brivaracetam was well tolerated. Higher frequencies of somnolence, dizziness, fatigue, influenza, insomnia, nasopharyngitis, vomiting, diarrhea, urinary tract infection, and nausea were reported in all treated groups than in the placebo group.

Psychiatric side effects including irritability and increased anxiety are associated with levetiracetam. Therefore, it is important to understand whether brivaracetam results in these adverse events. In this study, the most common reason for discontinuation was psychiatric disorders. No dose correlation was found. The authors suggest that when comparing nonpsychotic behavioral adverse events such as irritability and aggression the numbers reported appeared to be less in this study of brivaracetam than in prior published reports of levetiracetam. As no head to head studies have been done, this claim should be viewed with caution.

Interestingly a subanalysis of levetiracetam use (either concomitant use, prior levetiracetam exposure, or levetiracetam naïve) compared with placebo revealed a greater effect of brivaracetam among those who had received levetiracetam before or were levetiracetam naïve. Although there was only a limited group receiving concomitant levetiracetam (<20%), this finding has been reported in other studies (2, 3, 10, 11). These results suggest that using levetiracetam in combination with brivaracetam decreases the effect of brivaracetam. If brivaracetam is later approved, this will need to be considered when adding brivaracetam to a multidrug regimen.

The results of this phase III study suggest that concomitant brivaracetam at a dose of 50 mg/day results in significant reductions in seizure frequency as compared with placebo. No significant tolerability issues were found in any of the brivaracetam-treated groups. These efficacy findings were not however, reproduced in the other recently published phase III study (2). Using a similar design, subjects treated with brivaracetam 20, 50, 100 mg/day were compared with a placebo group. In that study, brivaracetam treatment at 50 mg/day had to demonstrate superiority over placebo in order to meet the primary efficacy endpoint. The primary efficacy analysis was not significant. Treatment with 100 mg/day did reach significance when compared with placebo. Further ongoing prospective studies using higher daily doses may clarify the minimally effective dose. Given the mixed results, the effectiveness of the 50 mg/day dose remains in question.



by Alison M. Pack, MD, MPH

References

1. Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. *Epilepsia* 2014;55:57–66.
2. Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. *Epilepsia* 2014;55:47–56.
3. Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. *Epilepsia* 2014;55:38–46.
4. Crowder KM, Gunther JM, Jones TA, Hale BD, Zhang HZ, Peterson MR, Scheller RH, Chavkin C, Bajjalieh SM. Abnormal neurotransmission in mice lacking synaptic vesicle protein 2A (SV2A). *Proc Natl Acad Sci U S A* 1999;96:15268–15273.
5. van Vliet EA, Aronica E, Redeker S, Boer K, Gorter JA. Decreased expression of synaptic vesicle protein 2A, the binding site for levetiracetam, during epileptogenesis and chronic epilepsy. *Epilepsia* 2009;50:422–433.
6. Kaminski RM, Matagne A, Leclercq K, Gillard M, Michel P, Kenda B, Talaga P, Klitgaard H. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. *Neuropharmacology* 2008;54:715–720.
7. Gillard M, Fuks B, Leclercq K, Matagne A. Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties. *Eur J Pharmacol* 2011;664:36–44.
8. Zona C, Pieri M, Carunchio I, Curcio L, Klitgaard H, Margineanu D-G. Brivaracetam (ucb 34714) inhibits Na_v current in rat cortical neurons in culture. *Epilepsy Res* 2010;88:46–54.
9. Matagne A, Margineanu D-G, Kenda B, Michel P, Klitgaard H. Anti-convulsive and anti-epileptic properties of brivaracetam (ucb 34714), a high-affinity ligand for the synaptic vesicle protein, SV2A. *Br J Pharmacol* 2008;154:1662–1671.
10. French JA, Costantini C, Brodsky A, von Rosenstiel P. Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. *Neurology* 2010;75:519–525.
11. van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. *Epilepsia* 2013;54:89–97.